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(57) Abstract

Disintegratable tablets for oral administration are made from a three pellet system. One type of pellet contains drug, another is soft and another includes a disintegrant allowing the tablet to disintegrate in the stomach. The drug pellets are preferably coated, for instance with a controlled release binder. The soft pellets preferably contain an ester of a fatty ester. The disintegratable pellets preferably comprise a water-insoluble inorganic powder, such as barium sulphate, iron oxide, magnesium oxide or calcium carbonate. The soft pellets deformed during the tabletting procedure to minimise damage to the drug containing pellets, for instance minimising disruption of the coating. The disintegrant pellets mean the release characteristics from the drug pellets are retained.

anvat een tablet bestaande
uit drie soorten pellet
– activa
– deformable → [illegible]
– desintegr.

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PREPARATION OF TABLETS COMPRISING A COMBINATION OF ACTIVE PELLETS, DEFORMABLE PELLETS AND DISINTEGRATABLE PELLETS

The present invention relates to a process for preparing tablets which, upon introduction into a liquid disintegrate, releasing pellets containing active ingredients into the liquid. The active ingredient is generally released in a controlled manner, preferably over an extended period of time, into the liquid environment. The active ingredient may be a pharmaceutically active ingredient, a compound for water treatment, a pesticide or herbicide, or nutrient. The products are of particular utility as orally administered controlled release pharmaceutical compositions.

Controlled or extended release compositions which comprise a plurality of pellets each containing active ingredient are well known. The content of individual pellets can be adapted by altering the binder system, the active ingredient, the excipients or diluents, or by varying the size or density, with ease, in order to obtain the desired characteristics. It is also known to include pellets of different types in a single dosage form. For instance this may allow the incorporation of two different active ingredients, or the incorporation of active ingredient to be released at different times, rates or even position in the GI tract (for oral administered pharmaceutical compositions). The pellets may or may not disintegrate after a given period of time in the position where the active ingredient is desired to be released. For orally administered pharmaceutical compositions, provided the pellets are sufficiently small, they can be expelled into the lower regions of the GI tract.

Pellets are generally incorporated into a form of a dosage for instance by filling them into a capsule which can rupture or dissolve in the use location. For orally administered pharmaceutical compositions capsules are usually formed of gelatin, which dissolves in the stomach to release pellets into the gastric juices. There are, however, problems with capsules of this type. Filling the

capsules, especially where there are pellets of different types, involves complicated procedures to ensure exact quantities of the pellet(s) are filled. Capsules are considered by many to be less easy to swallow than tablet form ingredients. Capsules may be open to contamination since they are fairly readily opened and re-closed. Some patients may have an adverse reaction to gelatin, the usual material from which capsules are formed.

It would be desirable therefore to provide compositions including pellets containing active ingredient in the form of tablets. Tabletting equipment is more readily available and faster to operate than capsule filling machinery. The tablets do not have many of the problems associated with capsules mentioned above. The problem with attempting to make tablets, using normal techniques to tablet pre-formed pellets is that when the pellets and any excipient are placed in the die and subjected to pressure, some or all of the pellets can fragment (disintegrate). Upon contact of the tablet with liquid the extended or controlled release properties of the original pellets are lost or significantly reduced. Examples of proposals to tablet pellet form active ingredient are in, for instance, EP-A-0,173,210, EP-A-0,080,341 and EP-A-0,265,061, but without details as to how this may be achieved.

There have been suggestions to incorporate pellets into tablets in the prior art. For instance in EP-A-0,119,480 pellets are introduced into a tabletting apparatus in the presence of various excipients in powder form. In Eur J Clin Pharmacol (1988) 33 [suppl] S3-S7 Sandberg et al describe a tablet formed from pellets of metoprolol succinate. The tablet is intended not to disintegrate, but to remain as a single unit during GI transit. There is little detail as to how the tablets are formed, but it is stated that the pellets containing active ingredient and coated with a polymeric membrane are compressed together with excipient granules to form a

tablet. The content of the excipient granule is not disclosed.

In "Design of an Oral Sustained Release Drug Delivery system comprising polymer coated pellets compacted into tablet" Dyer et al describe the production of a tablet formed from pellets containing active ingredient. The pellets are coated with a polymer which forms a controlled release membrane and on oral administration of the tablets intact polymer coated pellets are released in which the controlled release membranes are preserved. The pellets are formed by extrusion-spheronisation of a mixture of 80% ibuprofen and 20% Avicel (microcrystalline cellulose). The spheres were subsequently coated with a film including triethyl citrate plasticiser to help form a coherent film around the pellets. The pellets were then introduced into a tabletting machine with a mixture of excipients including lactose particles, microcrystalline cellulose and magnesium stearate, the total amount of excipient being adequate to fill the void volume (being more than 40% by weight of total mixture). Release profiles of active ingredient from the tablets indicate that the film coat is damaged during the tabletting procedure, resulting in increase in release rate. Scanning electron microscopy showed that damage was incurred by pellets during the tabletting operation, particularly at the tablet surface.

A difficulty with a process such as described by Dyer et al is that mixing of powders and pellets is difficult. The components tend to separate out on storage or transport so that special precautions have to be taken during the tabletting procedure to ensure that a constant mixture is supplied to the tabletting die.

In Pharmaceutical Research, October 1993 (supplement) 10(10) S1-S454 D L Mount and J B Schwartz describe forming tablets from drug spheres (details of which are not given), and either cushioning powder or spheres containing a mixture of glyceryl palmitostearate and microcrystalline cellulose. It was found that tablets formed from pellets

mixed with powder did not disintegrate completely although there was some reduction in drug release rate. The spheres containing glyceryl palmitostearate however protected the drug spheres whilst allowing disintegration into a multi-particulate system (that is in which intact drug spheres are released into a liquid). There was a reduction in the rate of release of drug.

Beckert et al, International Journal of Pharmaceutics 143(1996) 13 to 23 describe formation of tablets from hard coated drug containing pellets and softer pellets formed by a powder layering method using sucrose crystals as a seed, the powder consisting of lactose, polyvinyl pyrrolidone and Aerosil (colloidal anhydrous silica), and a binder consisting of a solution of an acrylic polymer and sucrose in water. The soft pellets deform slowly under a load, the maximum applied force varying from 2 to 6 newtons. The authors found that the type and thickness of the film forming polymer used to coat the drug containing pellets was the most important parameter form minimising rupture of the coatings in the tabletting procedure. The successful film coatings had an elongation at break as determined by Lehmann and Süfke (1995) Pharm. Res., 12(9) S137, of 50% or more.

The present inventors have found that a process in which drug spheres are tabletted with deformable pellets such as pellets comprising glyceryl palmitostearate and microcrystalline cellulose increase the disintegration time of the tablets to an undesirable extent. Furthermore the physical properties of the tablets themselves, in terms f their tensile strength and crushing force are low and the tablets tend to be relatively low density and of high porosity.

According to the invention there is provided a new process of forming a tablet containing an active ingredient in which:

1) active pellets having a mean diameter d_a in the range 0.5-5 mm comprising the active ingredient and an

excipient and which have a crushability of c_a of at least 0.5 kgf;

2) deformable pellets having a mean diameter d_d in the range (0.5-2) d_a and which have a crushability c_d of less than 0.5 c_a; and

3) disintegratable pellets having a mean diameter d_i in the range (0.5-2) d_a and which comprise a disintegrating component;

are mixed together and tabletted in a tabletting die, in which disintegrating component is selected such that upon contact of the tablet with a body of aqueous liquor the tablet disintegrates to allow dissolution of active ingredient into the liquor.

The invention thus uses a triple pellet system. A drug pellet is protected from damage during the tabletting procedure whilst retaining the requirement that the tablet should disintegrate to release drug pellets into a liquid by a combination of two pellets, a deformable pellet and a disintegratable pellet. The deformable pellet probably provides physical protection/cushioning for the active pellets during the tabletting procedure, whilst the disintegratable pellets allow the tablet itself to disintegrate upon the tablet being added to a liquid.

The invention is of most benefit for oral pharmaceutical compositions, that is where the active ingredient is a pharmaceutically active ingredient. However the invention may also be of value for the compounding of active ingredients for water treatment, pesticides or herbicides or nutrients, for plants, animals or humans.

To achieve the protection or cushioning of the active pellets in the tabletting procedure the crushability of the deformable pellets should generally be less than 0.3 c_a, more preferably less than 0.2 c_a. The crushability of the drug pellet is preferably at least 1.0 kgf, more preferably at least 1.2 kgf.

The crushability is determined using an apparatus as illustrated in figure 1, for instance a CT40 Engineering Systems apparatus, used as standard pharmaceutical crushability test. The device supplies a force over the pellet when the upper part moves down at a constant rate. The force increases until the pellet (or tablet) is crushed. The value of the maximum force applied is recorded. The crushability is the mean of a number of tests on similar pellets (or tablets).

The active pellets contain an excipient which contributes to the desired physical properties, particularly crushability, of the pellet. The excipient is selected according to its suitability for the intended use of the tablets, so that for a tablet to be used as a pharmaceutical dosage form, the excipient should be pharmaceutically acceptable. The excipient may comprise a mixture of components to provide the desired properties. For instance it may comprise a polymeric binder material. Suitable binders are, for instance, cellulosic-based binders, especially microcrystalline cellulose. The excipient may comprise furthermore a diluent, such as a sugar, especially lactose.

The active pellets are generally provided with controlled release properties, such that they release the active ingredient over an extended period of time when dispersed in a liquid. The controlled release binder may comprise a matrix binder, which is dispersed throughout the body of the pellet. The invention is of particular value where the controlled release binder consists of a surface coating on the pellets. The coating generally comprises a film-forming binder, usually comprising a polymer binder, for instance a synthetic or naturally derived polymer binder. Preferably the coating is an enteric coating that is which is resistant to gastric and intestinal juices, preferably one which gives controlled release into gastric and intestinal juices. Commercially available binders for coating, such as celluose ethers or esters, eg cellulose

acetate phthalate or acrylic resins, or gums or sugars may be used. Preferably the material from which the coating is formed is applied from an aqueous binder although solvent applied coatings may also be used. The coating level is selected so as to achieve a suitable drug release profile.

The triple pellet system of the present invention allows the active pellets to remain intact upon the tabletting process being carried out. It is believed that the coating around an active pellet will remain relatively undamaged. In order to minimise damage it may desirable to incorporate a plasticiser into any coating of the active pellets in order to minimise damage to the coating. The plasticiser may be an internal (built-in to the binder polymer) plasticiser or an external plasticiser, that is a separately added component to the coating mixture. Preferably the coating formed is such that a film of the material has an alongation at break of at least 10%, preferably at least 25%, more preferably 50% or more.

The deformable pellets for use in the present invention generally comprise a material which is a solid at temperatures likely to be experienced during manufacture and storage of the tablet product, but which is relatively easily deformed when subjected to pressure. The present inventors believe that the material is one which is easily plastically deformed and is, for instance, an ester, ether or, preferably, salt of a fatty acid, for instance a derivative of an acid having an alkyl chain length of at least 12, preferably around 18, carbon atoms. Suitable components are, for instance, glyceryl mono-, di- or tri-esters of palmitic and/or stearic acid or mono- or di-valent metal salts of fatty acids such as stearic and palmitic acid. The material may often have a melting point of no more than 70°C, though preferably more than 25°C eg in the range 40-60°C.

The deformable pellets generally comprise an additional binder to assist in the formation of the pellets and provide suitable mechanical properties of the

properties. A suitable binder is a cellulosic derivative, especially microcrystalline cellulose.

In the deformable pellets the plastically deformable component is generally present in an amount in the range 10 to 80%, more preferably 20 to 50% by weight, based on dry components. The binder is generally present in an amount in the range 5 to 75%, for instance in the range 10 to 50%. The ratio of plastically deformable component to binder is preferably in the range 1:(0.2 to 2) more preferably in the range 1:(0.5 to 1). The soft pellets may contain a diluent, for instance which may provide the pellets with a desired density. Diluents may be, for instance, water-insoluble inorganic powders such as barium sulphate, calcium carbonate, magnesium carbonate, etc. The diluent may be present in an amount up to 85%, preferably no more than 60%, usually at least 20%.

The disintegratable pellets comprise a disintegrating component which allows the tablet to disintegrate upon contact with a body of liquid, usually an aqueous liquid, for instance gastric juices in the stomach of a patient to whom the tablet has been administered. Suitable disintegrating components are selected so as to provide the change in physical properties, that is cohesion of the components in the tablet, upon addition to liquid, usually aqueous liquid. The disintegrating components may be readily soluble in the liquid, its dissolution leading to its removal from the tablet, with adhesion of the remaining components to one another being destroyed. Alternatively the disintegrating component may be swellable in the liquid, swelling leading to fracturing of the tablet. However most swellable organic pharmaceutically acceptable compounds can lead to increased cohesion between pellets.

Alternatively, and most preferably, the component may be one with low adhesive and cohesive properties, especially in the presence of the liquid, so that the interfacial characteristics lead to a disintegration of the pellets and hence the tablets upon addition to the liquid.

Suitable disintegrating agents which have low adhesive and cohesive properties are generally water insoluble inorganic salts such as barium sulphate, calcium carbonate, calcium phosphate, iron oxide, magnesium oxide, magnesium carbonate and dicalcium hydrogen phosphate.

The disintegrating pellets generally comprise a binder, selected so that the pellets have the desired mechanical properties to allow them to be formed into tablets and allow the disintegrating component to have its desired effect upon addition of the tablet to a liquid. The binder is suitably a cellulosic binder, for instance microcrystalline cellulose.

In the disintegrating pellets the disintegrating is preferably present in an amount in the range 20 to 95% by weight (based on dry materials) preferably in the range 40 to 80% by weight. Binder is generally the only often component of these pellets although and inert dilient may be incorporated. The amount of binder is preferably 80 to 5% by weight preferably 60 to 40% by weight.

The use of three different types of pellets, without incorporating any powder components, provides advantages from the processing point of view. The pellets preferably have similar sizes so that they can be blended and stored with minimal difficulties in terms of component separation. The sizes and densities are selected so as to optimise the mixing characteristics. The present inventors have found that the size is the most important factor and for this reason the diameter of each of the deformable pellet and disintegratable pellet should be in the range half to twice the diameter of the active pellet. Preferably the mean diameter of each of those pellets, d_d and d_i, is in the range (0.75 to 1.5) d_a, more preferably in the range (0.9 to 1.2) d_a. The relative densities of the pellets should be such that no pellet is more than three times the density of another pellet, more preferably no more than 2.5 times the density of another pellet.

Although the pellets may be formed by granulating techniques, in which a mixture of powders is mixed together and contacted with a granulating liquid whilst being mixed, it is preferable for the pellets to be made by extrusion spheronisation. The pellets may all be made by the same technique or may be made by different techniques.

The pellets preferably have a mean diameter (weight average) in the range 0.5-5 mm, more preferably in the range 0.7-2 mm. Preferably the pellet a relatively homogeneous in terms of size, for instance having an interquartile range is less than one half, more preferably less than one quarter of the mean.

The pellets are used in a weight ratio, active pellets:deformable pellets:disintegrating pellets in the range 1:(0.2-5.0):(0.2-5.0), preferably 1:(0.5-2.0):(0.5-2.0). It is desirable to use as much active pellet as possible. The amount of active pellets is generally at least 20% and less than 50% by weight of the total pellet weight. The amount of disintegrating pellets is preferably at least 20% by weight. The amount of deformable pellet is preferably at least as high as the amount of disintegrating pellets.

Whilst tabletting may be carried out in any conventional tabletting machine. The present inventors have found that it is possible to tablet under relatively high compression pressures without destroying the active pellets. For instance the pressure may be up to 200 MPa, although adequate physical properties are generally achieved with compression pressures up to 150 MPa although pressures lower than 130 MPa are preferred. The pressure should preferably be above 75 MPa, more preferably above 100 MPa. With lower compression pressures, the tablet may have inadequate tensile strength and crushability. Furthermore the tablets tend to be extremely friable, fragmenting to an undesirable extent when subjected to a friability test.

It is preferred for the die of the tabletting machine to be a circular cylindrical die. Although it may have a degree of concavity, for instance up to 2.0 mm, it is preferred for the device to have 0 or very low concavity. The invention has been found to be suitable for producing tablets of any desired diameter, although seems to be of particular benefit for tablets with a relatively low surface area to volume ratio, that is with relatively high diameters. The diameter is, for instance, more than 10 mm, for instance in the range 10-25 mm.

The invention is illustrated further in the following examples:

Example 1.1 - Preparation of Indomethacin Pellets

Indomethacin containing spheres were produced by mixing indomethacin, lactose and microcrystalline cellulose powders in the relative proportions (by weight) shown in table 1, for 20 minutes in a Turbula mixer (T2C). The mixed powder was then transferred into a planetary mixer (Kenwood Chef) where water (3.36 parts per 8 parts powder) was added whilst stirring at 90 rpm for 10 minutes. The wet mass formed was allowed to stand for 12 hours in a sealed plastic bag to ensure good water distribution before further use.

The mass was then extruded using a ram extruder (barrel with 25 mm diameter) mounted in a mechanical press (Lloyd instruments, MX50) which was fitted with a 50 kN load cell. The cross head was displaced at 400 mm/minute. The wet mass was extruded through a die having a diameter of 1 mm, with a length/diameter ratio selected so as to provide suitable diameter spheres. The extrudate was subsequently extrusion spheronised to produce spheres having diameter in the range 1.0-1.4 mm in diameter.

TABLE 1

Example	Parts by Weight		
	IND	LAC	MCC
1.1.1	0	5	3
1.1.2	0.25	4.75	3
1.1.3	0.5	4.5	3
1.1.4	1.0	4.0	3
1.1.5	2.0	3.0	3
1.1.6	3.0	2.0	3

IND = indomethacin (Bechpharm - medium volume particle diameter 57 .0 ± 1.86 μm

MCC = microcrystalline cellulose (Ariel PH 101 FMC Corp, median volume diameter 16.8 ± 0.35 μm)

LAC = lactose (EP - Meggle-Wasseburg - median volume diameter 53.8 ± 0.54 μm)

1.2 - Preparation of Deformable Pellets

Deformable pellets were produced using the same technique as example 1.1, from a mixture of 3 parts glycerylmonostearate, 5 parts barium sulphate and 2 parts microcrystalline cellulose, with 3 parts water being added in the planetary mixer.

1.3 - Preparation of Disintegratable Pellets

Disintegratable pellets were formed using the same technique as example 1.1. using a mixture of 8 parts barium sulphate powder and 2 parts microcrystalline cellulose with 3 parts water added to the planetary mixer.

Example 2 - Analysis of Uncoated Spheres from Example 1

The spheres produced in examples 1.1 to 1.3 were analysed for their particle size and size distribution (using sieve analysis), crushing force, density (using a Beckman air pycnometer and release of indomethacin by dissolution test according to US Pharmacopoeia XXI

(phosphate buffer 37°C), using a Pharmatest dissolution tester, the speed of the paddles being set at 100 rpm and pH being 7.4. The indomethacin dissolution tests were run in triplicate and were found to produce results without large standard deviations.

The results are shown in Table 2.

TABLE 2

Example	Crushing Force (kgf) (n=10)	Density (gcm^{-3}) (n=5)	Poros. (%)	Diameter/IQR (mm)		MDT (h)
1.1.1	1.85 ± 0.32	1.52 ± 0.01	1.6	1.34	0.24	-
1.1.2	1.44 ± 0.18	1.47 ± 0.00	4.4	1.29	0.26	0.9
1.1.3	1.49 ± 0.26	1.46 ± 0.01	4.7	1.21	0.36	N/A
1.1.4	1.17 ± 0.24	1.45 ± 0.01	4.7	1.07	0.28	2.1
1.1.5	1.40 ± 0.17	1.45 ± 0.01	3.3	1.27	0.32	N/A
1.1.6	1.21 ± 0.16	1.44 ± 0.01	2.5	1.31	0.26	3.4
1.2	0.24 ± 0.09	1.42 ± 0.02	38.0	1.25	0.43	-
1.3	0.49 ± 0.15	3.14 ± 0.03	15.3	1.39	0.19	-

IQR = interquartile range

n = number of pellets tested

MDT = mean dissolution time (that is the centre of gravity of the area under the dissolution time profile)

Example 3 - Coating of Indomethacin Spheres

Indomethacin containing spheres from example 1 were coated in a fluid bed coater (Aeromatic AG) according to the following conditions.

- amount of spheres used per batch (g): 20
- inlet air temperature (°C): 60
  outlet air temperature (°C): 40
  inlet air pressure (mm column of water): 35
  inlet air volume (m^3h^{-1}): 100
- atomised air pressure in the nozzle (bar): 0.2
  coating feeding rate to the nozzle ($mlmin^{-1}$): 1.5
- temperature of the suspension with polymer (°C): 60

Each coating cycle took, in average 20 minutes.

The coating solution consisted of ethyl cellulose (EC) (Surelease - Colorcon Limited) dissolved in water, at concentrations specified in Table 3.

The coated pellets were subjected to the dissolution test and the results of the mean dissolution time are shown in Table 3, compared to the uncoated pellets.

TABLE 3

Example	Parts Indomethacin (in total 8 parts uncoated weight	EC Concentration %	MDT (h)
3.1.1 (1.1.2) 3.1.2 (1.1.4) 3.1.3 (1.1.6)	0.25 1.0 3.0	0 0 0	0.9 2.1 3.4
3.2.1 3.2.2 3.2.3	0.25 1.0 3.0	1.5 1.5 1.5	1.62 4.41 5.45
3.3.1 3.3.2 3.3.3	0.25 1.0 3.0	3.0 3.0 3.0	2.63 5.42 6.51
3.4.1 3.4.2 3.4.3	0.25 1.0 3.0	7.0 7.0 7.0	3.03 2.90 2.52

The indomethacin release profile as a function of time for the uncoated, and three types of coated sphere are illustrated in figures 2-5.

From the results it can be seen that the ethyl cellulose coating slows down the release of indomethacin from the pellets during the dissolution test.

Example 4 - Forming Tablets from Spheres Produced in Example 1

Indomethacin containing pellets (spheres) produced in examples 1.1.2 to 1.1.6, deformable pellets (spheres) formed in example 1.2 and disintegratable pellets (spheres) formed in example 1.3 were mixed in a Turbula mixer for 3 minutes at 20 rpm and tabletted in a tabletting machine. Two machines were used for the tests, an Instron universal testing instrument and a Manesty F3 instrumented tabletting

machine. The effect of varying the relative proportions of the different types of sphere, the compression pressure, the punch diameter and the concavity were determined.

The tablets produced were subjected to tests of the density, the porosity, the crushing force (tested as for the spheres), the tensile strength (calculated from the crushing force), the friability, measured in a Roche Friabilitor at 25 rpm for 4 minutes, the disintegration time, taken as the time between the tablet coming into contact with water and collapsing releasing the spheres, measured in a Manesty tablet disintegration test unit, and the mean dissolution time of indomethacin determined as described by Brockmayer et al (1982) Drug Research, 32, 248-251.

The content of the various components and the conditions used are shown in Table 4. The results of the tests carried out on tablets produced in the Manesty machine are shown in Table 5. The results of the tablets produced in the Instron machine are shown in Table 6.

TABLE 4

Parameter Varied	Example 4.(1/2)	IND Spheres Example	Parts Active Sphere in tablet	Parts Sphere in Tablet 1.3	Parts Sphere in Tablet 1.2	Compression Pressure MPa	Die Diameter mm	Di Concavity mm
Drug Load	1	1.1.6	25	50	25	108	12	0.0
	2	1.1.5	25	50	25	108	12	0.0
	3	1.1.4	25	50	25	108	12	0.0
	4	1.1.3	25	50	25	108	12	0.0
	5	1.1.2	25	50	25	108	12	0.0
Sphere Proportions	6	1.1.4	15	50	35	108	12	0.0
	7	1.1.4	35	50	15	108	12	0.0
	8	1.1.4	50	50	0	108	12	0.0
	9	1.1.4	25	0	75	108	12	0.0
	10	1.1.4	25	25	50	108	12	0.0
	11	1.1.4	25	75	0	108	12	0.0
Compression Pressure	12	1.1.4	25	50	25	43	12	0.0
	13	1.1.4	25	50	25	65	12	0.0
	14	1.1.4	25	50	25	87	12	0.0
	15	1.1.4	25	50	25	130	12	0.0
	16	1.1.4	25	50	25	170	12	0.0
Die Diameter	17	1.1.4	25	50	25	108	10	0.0
	18	1.1.4	25	50	25	108	8	0.0
Die Concavity	19	1.1.4	25	50	25	108	12	1.5
	20	1.1.4	25	50	25	108	12	2.8

TABLE 5

Exampl	Ejection Force (N)	Density (g ml^{-1})	Porosity (%)	Crushing Force (kgf)	Tensile Strength	Friability (%)	Disintegration Time (min)	MDT (h)
4.1.1	121	1.89	38.26	7.22	0.082	3.37	3.5	2.28
4.1.2	146	1.91	30.56	8.58	0.100	2.80	3.5	1.92
4.1.3	136	1.97	28.29	7.75	0.090	4.11	3.5	1.64
4.1.4	138	2.12	22.88	8.77	0.102	6.22	3.5	1.10
4.1.5	104	1.80	24.85	8.03	0.093	4.33	5.0	0.94
4.1.6	122	2.03	27.79	7.49	0.088	5.69	4.5	1.87
4.1.7	132	2.11	22.06	9.17	0.108	61.2	0.01	1.26
4.1.8	863	2.10	19.90	4.37	0.050	100	0.01	0.98
4.1.9	133	1.48	23.38	7.95	0.060	1.21	60	2.82
4.1.10	168	1.69	27.94	9.09	0.086	3.51	30	2.43
4.1.11	640	2.55	19.61	3.50	0.048	100	0.01	1.21
4.1.12	97	2.21	19.82	2.58	0.026	100	0.01	1.35
4.1.13	87	2.08	24.33	5.30	0.056	36.4	0.01	1.46
4.1.14	141	2.26	17.71	6.13	0.071	100	3.0	1.40
4.1.15	158	2.12	23.09	10.3	0.120	1.18	3.5	1.44
4.1.16	977	2.07	24.84	10.6	0.120	1.14	3.5	1.47

TABLE 6

(1)	Density (g ml^{-1})	Porosity (%)	Crushing Force (kgf)	Tensile Strength (Nm^{-2})	Friability (%)	Disintegration Time (min)	MDT (h)
4.2.1	2.29	16.4	10.4	0.102	0.7	2	2.56
4.2.2	2.30	16.2	9.0	0.100	1.0	2	2.29
4.2.3	2.38	17.5	9.4	0.104	1.0	2	1.91
4.2.4	2.28	17.2	9.6	0.105	1.0	2	1.13
4.2.5	2.30	16.5	9.6	0.105	1.2	2	0.90
4.2.6	2.47	11.9	8.7	0.096	1.9	2	1.85
4.2.7	2.30	14.7	10.2	0.111	1.6	2	1.65
4.2.8	2.34	10.5	13.8	0.148	0.5	0.01	1.16
4.2.9	1.68	12.9	6.0	0.052	3.5	30	3.42
4.2.10	1.95	16.6	6.7	0.065	1.4	10	2.25
4.2.11	2.79	11.7	12.2	0.150	1.7	0.01	1.45
4.2.12	2.26	17.8	6.1	0.062	20.6	2	1.91
4.2.13	2.31	16.0	6.2	0.065	3.8	2	1.92
4.2.14	2.26	17.8	8.4	0.090	1.9	2	1.80
4.2.15	2.28	17.1	8.3	0.091	1.3	2	1.75
4.2.16	2.28	17.1	9.7	0.107	1.6	2	1.79
4.2.17	1.94	29.5	7.7	0.068	3.4	4	1.44
4.2.18	1.95	29.1	9.2	0.071	6.4	7	1.51
4.2.19	1.94	29.5	1.9	0.078	100	3	1.26
4.2.20	1.97	28.4	2.5	0.038	100	3	1.40

Comparing the results of 4.1.1 to 4.1.5 and 4.2.1 to 4.2.5 with the results of the mean dissolution times of the uncoated spheres of examples 1.1.2 to 1.1.6 (Table 2) it can be seen that tablets made from indomethacin containing spheres with a lower proportion of drug seem to have the same dissolution time for indomethacin as the uncoated pellets themselves. This is true both for tablets produced in the Manesty machine and tablets produced in the Instron machine. For tablets made from pellets having a medium amount of indomethacin (1 part in 8 parts of the drug pellet) there is a reduction in the value of MDT. This reduction is less for the Instron-produced tablets. For the higher drug load tested (3 parts in 8 of the drug pellet) the proportional reduction in the MDT is somewhat higher, although the MDT of the tablets is still reasonably high. These results suggest that the drug pellets are being damaged only to a small extent by the tabletting procedure. The results indicate further that the tablets produced on the Instron machine are damaged to a lesser extent than those produced on the Manesty machine.

The results of experiments 4.1.6 to 4.1.11 and 4.2.6 to 4.2.11 show the effects of changing the proportions of the deformable pellets (of example 1.2) and of disintegration pellets (of example 1.3). Examples 9 and 10 contain, respectively, no disintegratable pellets and a low amount (25 parts per 100 parts) of disintegratable pellet. The results of the analyses of the tablets show that these tablets have a greatly increased disintegration time. The tablets produced on the Instron machine, with no disintegratable pellets, have a disintegration time of 30 minutes, whilst those produced in the Manesty machine have a time of 60 minutes. Since it is in general desirable to have a disintegration time of less than 5 minutes, these results illustrate the advantage of incorporation of disintegratable pellets. It further appears from the results of examples 9 and 10 that the tensile strength of tablets formed with low amounts or no disintegratable

pellets are unsatisfactory. Furthermore it is to be noted that the MDT values for the tablets produced without disintegratable pellets is high, the increase as compared to the standard composition (composition 4.1.3 and 4.2.3) not being explained solely by the increase in disintegration time. This indicates that the remaining components of the tablet, that is the glyceryl monostearate-containing deformable pellets, must affect the release of indomethacin from the pellets. This may be by the formation of a barrier around the indomethacin pellets. The formation of such a barrier may in some circumstances be desirable.

From the results of tests 7, 8 and 11, the effect of putting low or no deformable pellets into the mixture can be seen. Although the disintegration time for those tablets is relatively low, it can be seen from the results (4.1.7 etc) that the friability values for the tablets produced in the Manesty machine are extremely poor. The tensile strength values for examples 8 and 11 produced in the Manesty machine are rather low, which is undesirable. It is apparent that the changes in MDT are not explicable solely by changes in disintegration time.

Examples 4.1.6 and 4.2.6 indicate that the relative proportions of disintegratable and deformable pellets can be varied to some extent, although it seems that it is desirable for the amount of disintegratable pellet to be higher than the amount of deformable pellet and that the total amount of disintegratable pellet is more than 25% of the total weight of pellets used.

The results of experiments 4.1.12 to 4.1.16 and 4.2.12 to 4.2.16 show the effect of changing the compression pressure on the properties of the tablet. For the Instron machine it is interesting to note that the mean dissolution time changes very little with changing pressure, although it is reduced slightly with the higher compression pressures. The disintegration time is changed hardly at all, although for the Manesty produced tablets, at very low

pressures, the disintegration time is very low. However the results show that for the low compression pressure examples the tablets have an undesirable high friability result and undesirably low tensile strength and crushing force values. The MDT values are maintained at higher values in the Instron tester than in the Manesty machine. From these results it seems that it is desirable to a tabletting device in which the punch moves slowly and, in order to obtain suitable mechanical properties of the tablet it is desirable to use pressures of greater than 100 MPa.

The ejection force values in Table 5 show that the present invention provides compositions which are acceptable from a manufacturing point of view. When deformable pellets are omitted (examples 4.1.8 and 4.1.11) the ejection forces are unacceptably high even if the compressive pressure used to form the tablets is within a range that, with deformable pellets, would give acceptable results (ie less than about 150 or 130 MPa).

From the results of 4.2.17 and 4.2.18 it seems that it is desirable for a die having a relatively large diameter to be used. Using a die with a diameter of 12 mm, the MDT value is higher, whilst the friability and tensile strengths values are better.

<u>Example 5</u>

This example investigates the influence of the disintegrant type and proportion of the properties of tablets.

Drug pellets, soft pellets and disintegrant pellets were each formed using extrusion spheronisation pelletisation techniques. The model drug in this system was riboflavin. For the disintegrating pellets, the disintegrant material specified in Table 7 below was used in the amount specified in the table. The soft pellets were of constant formulation formed of 5 parts barium sulphate, 2 parts glyceromonostearate, 3 parts Avicel (microcrystalline cellose) PH 101 and 3 parts water. The

drug pellets were the same throughout the experiment and were made from 5 parts of a mixture of riboflavin and lactose, 5 parts Avicel PH 101 and 6 parts water. The pellets, after extrusion spheronisation were dried but not subsequently coated.

The pellets were mixed in the proportion set out in Table 8 below by hand in plastic bags for a few minutes before being compressed in an instrumated single punch press (Manesty) equipped with round flat faced punches and a 10 mm diameter die. The upper punch force was kept constant at 2.5 kN. The fill volume was adjusted to obtain the required constant pressure but gave different fill weight for the different mixtures. The tablets were used to measure the breaking load, friability, content uniformity (that is the amount of drug per tablet) and disintegration time. The breaking load, friability and disintegration time are measured using the techniques described in Example 4 above. The drug content was measured by placing each tablet in 1 litre of distilled water in a paddle dissolution bath for 16 hours at 37.5°C and 100 rpm. The solutions were then placed in an ultrasonic bath for 2 minutes before absorbance was measured spectrophotometrically at 266 nm. Calibration curve of absorbence versus riboflavin concentration was made and used to determine the concentration of riboflavin for each tablet so analysed.

The results are shown in Table 9 below.

TABLE 7

Disintegrant Pellets		Proportions (weight)			Breaking Load	
No.	Disintegrant	Disintegrant	Avicel PH101	Water	Mean Kg of	Coefficient of Variant %
I	barium sulphate	5	5	6	1.37	7.6
II	barium sulphate	8	2	3	0.89	20.0
III	calcium carbonate	5	5	6	1.43	4.5
IV	magnesium oxide	5	5	6	4.63	13.1
V	iron oxide	5	5	6	1.55	5.1
soft pellets					0.18	20
drug pellets					1.62	6

TABLE 8

Mixture Number	Disintegrant pellets, %	Drug pellets, %	Soft pellets, %
1	0	40	60
2	15	40	45
3	30	40	30
4	45	40	15
5	60	40	0
6	30	20	50
7	30	30	40
8	30	50	20
9	30	60	10

TABLE 9

Example	Disintegrant Pellets	Mixture No.	Friability % n=5	Breaking Load	
				kg mean n=5	Variation coeff. %
5.1	I	1	0.3	4.55	10.2
5.2	I	2	24.8	2.38	22.8
5.3	I	3	45.3	1.68	30.9
5.4	I	4	64.2	0.59	53.9
5.5	I	5	85.3	0.50	36.2
5.6	I	6	10.8	3.42	29.9
5.7	I	7	13.3	2.86	31.6
5.8	I	8	41.5	2.17	24.8
5.9	I	9	58.6	2.10	54.7
5.10	II	2	0.4	3.89	18.7
5.11	II	3	10.1	3.42	28.2
5.12	II	4	53.7	2.17	12.2
5.13	II	5	77.1	1.08	40.7
5.14	II	6	0.7	4.31	15.8
5.15	II	7	6.2	3.81	16.3
5.16	II	8	33.7	2.49	15.6
5.17	II	9	63.4	1.76	23.2
5.18	III	2	1.7	4.50	10.2

TABLE 9 cont.

				Breaking Load	
Example	Disintegrant Pellets	Mixture No.	Friability % n=5	kg mean n=5	Variation coeff. %
5.19	III	3	22.3	2.77	23.8
5.20	III	4	49.9	1.61	28.6
5.21	III	5	82.7	0.50	22.9
5.22	III	6	1.4	3.63	21.7
5.23	III	7	1.3	3.73	14.8
5.24	III	8	33.2	2.82	24.7
5.25	III	9	46.3	2.75	30.2
5.26	IV	2	0.7	4.71	9.0
5.27	IV	3	7.8	3.67	21.1
5.28	IV	4	50.7	1.75	39.6
5.29	IV	5	76.6	0.90	55.0
5.30	IV	6	1.7	3.29	25.9
5.31	IV	7	2.8	3.41	10.6
5.32	IV	8	15.3	2.44	19.9
5.33	IV	9	28.3	4.22	22.5
5.34	V	2	0.4	3.50	9.0
5.35	V	3	9.6	2.11	19.8
5.36	V	4	46.8	0.54	31.9
5.37	V	5	61.6	3.25	35.0
5.38	V	6	1.5	3.09	12.3
5.39	V	7	3.3	2.97	25.3
5.40	V	8	25.2	1.77	9.9
5.41	V	9	47.1		38.3

TABLE 9 cont.

	Disintegration Time		Drug Level		
Example	S mean n=5	Variation coeff. %	Amount mean mg	Variation Coefficient	Theoretical mg
5.1	1765	35.9	3.35	9.2	3.91
5.2	886	11.7			
5.3	707	27.9			
5.4	306	23.6			
5.5	6	42.2			
5.6	1455	12.2	2.02	17.1	2.02
5.7	1350	16.4			
5.8	572	17.4			
5.9	339	38.4	5.13	3.3	6.17
5.10	1531	24.9			
5.11	1166	24.1			
5.12	301	11.8			
5.13	5	11.9			
5.14	879	7.2	1.72	10.4	2.22
5.15	811	32.2			
5.16	393	32.0			
5.17	340	48.8	5.46	6.4	6.26
5.18	1694	17.1			

TABLE 9 cont.

	Disintegration Time		Drug Level		
Example	S mean n=5	Variation coeff. %	Amount mean mg	Variation Coefficient	Theoretical mg
5.19	585	32.6			
5.20	259	16.3			
5.21	4	34.5			
5.22	1167	32.0	1.58	5.2	1.95
5.23	1108	10.9			
5.24	420	3.6			
5.25	297	20.8	5.15	4.4	5.65
5.26	1069	19.7			
5.27	807	4.7			
5.28	223	24.8			
5.29	6	29.5			
5.30	1267	24.7	1.20	13.0	1.85
5.31	593	33.5			
5.32	423	13.1			
5.33	261	31.8			
5.34	1198	10.7	2.79	8.8	3.64
5.35	826	22.0	2.72	6.6	3.80
5.36	409	23.8	3.30	6.5	3.99
5.37	4	31.7	3.06	6.8	4.20
5.38	860	22.8	1.63	7.3	1.96
5.39	925	24.7	2.04	10.1	2.88
5.40	606	19.7	3.84	3.0	4.74
5.41	208	20.3	4.48	4.4	5.69

The results show that tablets made from mixture number 5 having no soft pellets are completely unsatisfactory in that the friability values are very high, the breaking load values very low and the disintegration times close to zero. With between 10 and 20% soft pellets (formulations 4, 8 and 9), the friability and disintegration times increase whilst the breaking loads decrease. However for these pellets it appears that at least 30% of soft pellets are needed to achieve adequate friability and breaking load values. With regard to disintegrant pellets, the higher the proportion of such pellets, the higher the friability, the lower the breaking load and the shorter the disintegration time. The results also show that calcium carbonate provides results approximately equivalent to those using barium sulphate as the disintegrant at the same levels. The results show that 1:1 mixtures of barium sulphate and binder give better properties than the 4:1 barium sulphate:binder mixture in terms of friability and disintegration time.

Measurements for the weights of the tablets show that for all the formulations there is a low level of variation for tablets of the same mixtures. From the values of drug levels incorporated into the tablets, it can be seen that the coefficient of variation betweem the tablets is acceptably low, whilst the mean values of drug incorporated into tablets is close to the calculated theoretical level. Whilst the mixing technique is a manual one, it is believed that they indicate that pellet segregation during large scale manufacture could be reduced to an acceptable level.

Example 6

This example illustrates the incorporation of coated drug pellets into tablets in conjunction with soft pellets and disintegrant pellets with three of the disintegrants used in Example 5.

The drug pellets consisted of 80% theophylline, 15% microcrystalline cellulose and 5% lactose, pelleted by extrusion spheronisation, with pellets of size fraction 1.00 to 1.40 mm being recovered and dried. The drug

pellets were film coated in a fluidised bed coating apparatus using a bottom spray technique with an aqueous coating solution consisting of ethyl cellose (surerelease E-7-7050, Colorcon Limited) and methyl cellulose of viscose degrade 400 (Methocel A4C Premium, Colorcon Limited) with the ratio of methyl cellulose to ethyl cellulose being 0.16. The composition has been shown to give controlled release when applied in certain coating thickness to pellets containing theophylline (Yuen et al (1993), Drug Dev. Ind. Pharm., (1993) 855 - 874).

The soft pellets were made as an Example 1.2.

The disintegrant pellets were of types II, V and III in Example 5 above.

The pellets were mixed in different proportions as set out in Table 10 below in a plastic bag for several minutes before being compressed in the man of the single punch press used in Example 4 above, equipped with round normal concave faced punches and a die 12.5 mm in diameter. For each tablet 1,000 mg of pellets was weighed and manually filled into the die. Tablets from each formulation were used to measure the breaking load, friability, disintegration time and dissolution rate for thioethylene, using the methods described for Example 4 above. From the release curves the mean dissolution time, MDT, and its variants, VDT was calculated as described by Podczeck (1993) Int. J. Pharm. 97 (1993 93 - 100).

The results are shown in Table 11 below.

TABLE 10

Disintegrant Pellets No.	Disintegrant	Breaking Load	
		mean kgf	Coefficient Variation %
II	$BaSO_4$	0.88	9.9
III	$CaCO_3$	1.81	3.9
V	Fe_3O_4	2.26	17.9
Soft Pellets		0.16	21.1
Drug Pellets (uncoated)		1.78	15.2

TABLE 11

Example	Tablet Formulation number	Mixture No.	Dry Pellet Coat Thickness, %	Upper Punch force, kN	Friability %	Tablet Strength	
						mean kg	coeff. variation %
6.1	III	6	4.38	23.48	0.2	5.95	14.6
6.2	III	7	4.38	22.94	16.9	3.65	27.0
6.3	III	2	4.38	21.84	18.6	3.04	9.1
6.4	III	3	1.17	21.90	39.3	2.58	20.0
6.5	III	3	4.38	6.80	52.4	0.95	30.9
6.6	III	3	4.38	23.51	15.7	3.40	16.1
6.7	III	3	8.27	38.62	0.3	4.37	21.1
6.8	III	3	4.38	21.38	7.3	3.46	9.2
6.9	III	4	4.38	23.44	16.5	2.96	13.9
6.10	III	8	4.38	22.26	22.4	2.45	15.4
6.11	III	9	4.38	23.38	7.0	3.32	6.3
6.12	V	3	4.38	6.58	60.9	0.84	35.7
6.13	V	3	4.38	23.66	22.3	3.16	12.7
6.14	V	3	4.38	39.40	0.1	4.35	21.1
6.15	II	3	4.38	6.86	51.2	1.51	15.4
6.16	II	3	4.38	22.82	0.5	4.42	9.9
6.17	II	3	4.38	38.90	0	4.18	16.8
Drug Pellets:	Uncoated 1.17% 4.38 8.27	0 1.17 4.38 8.27					

TABLE 11 cont

Example	Disintegration Time		MDT		VDT	
	mean s	coeff. variation %	mean h	coeff. variation %	mean h	coeff. variation %
6.1	2250	23.5	2.68	10.4	3.77	28.6
6.2	1399	25.7	2.22	12.2	4.76	16.4
6.3	2217	25.6	2.87	4.0	6.37	4.1
6.4	932	16.8	1.09	2.5	0.49	2.2
6.5	722	35.4	1.79	8.8	2.04	40.0
6.6	1148	19.1	1.91	3.1	3.13	8.6
6.7	1274	20.4	2.13	7.9	2.57	13.1
6.8	746	29.4	2.46	3.4	6.41	4.2
6.9	268	19.5	1.40	0.1	2.07	32.4
6.10	591	18.6	1.55	3.0	3.39	42.5
6.11	327	15.7	1.30	3.8	5.11	4.7
6.12	723	21.5	1.88	5.1	5.00	26.8
6.13	1403	17.0	2.18	9.4	4.92	10.3
6.14	1616	34.4	2.46	6.4	3.75	10.5
6.15	887	26.4	2.31	1.8	4.63	18.6
6.16	1192	16.3	2.54	13.2	5.19	25.0
6.17	1425	32.5	2.69	9.6	5.85	23.2
Drug Pellets:			0.69	5.8	1.66	41.9
			1.60	2.6	1.19	11.1
			5.5	0.7	10.31	0.54
			6.07	0.35	10.47	0.49

As in Example 4, the present results show that it is necessary to achieve at least a minimum upper punch pressure in the tabletting machine to achieve adequate tablet strengths. Comparing the results of the mean dissolution times for the uncoated and coated pellets, it can be seen that coating thickness strongly influences release of drug. When the coated pellets are incorporated into tablets, again the coating thickness is the greatest influence on the mean solution time. The results do indicate that the mean dissolution time for tabletted pellets is lower than for the equivalent untabletted tablets but is still higher than the uncoated untabletted pellets. Example 4, on the other hand, showed that tabletting uncoated drug pellets reduced the MDT as compared to the untabletted uncoated pellets. Accordingly, whilst the coating of the drug pellets may be disrupted to some degree during the tabletting procedure, the coating retains a good deal of its controlled release properties.

It is to be expected that the use of coating materials which are more elastic would be likely to reduce the damage to the coating during tabletting and consequently allow better control of drug release properties.

CLAIMS

3 ingredients

1. A process for forming a tablet containing an active ingredient in which

i) active pellets having a mean diameter d_a in the range 0.5-5 mm comprising the active ingredient and an excipient and which have a crushability c_a of at least 0.5 kgf;

ii) deformable pellets having a mean diameter d_d in the range (0.5-2) d_a and which have a crushability c_d of less than 0.5 c_a; and

iii) disintegratable pellets having a mean diameter d_t in the range (0.5-2) d_a and which comprise a disintegrating component;

are mixed together and tabletted in tabletting die, in which the disintegrating component is selected such that upon contact of the tablet with a body of aqueous liquor the table disintegrates to allow dispersion of active pellets into the liquor.

2. A process according to claim 1 in which the excipient in the active pellet comprises a binder, preferably a cellulosic binder, more preferably microcrystalline cellulose, and optionally a diluent, for instance a sugar, preferably lactose.

3. A process according to claim 1 or claim 2 in which the active pellets are coated with film forming coating binder, preferably a controlled release coating.

4. A process according to any preceding claim in which the active ingredient is a pharmaceutical.

5. A process according to any preceding claim in which the deformable pellets contain a fatty acid ester, ether or salt, preferably having a melting point of not more than 70°C, and optionally also a cellulosic binder, especially microcrystalline cellulose.

6. A process according to any preceding claim in which the disintegrating component is a water-insoluble compound, preferably an inorganic salt, more preferably barium sulphate, calcium carbonate or dicalcium hydrogen phosphate.

7. A process according to any preceding claim in which the disintegrating pellets contain a binder, preferably a cellulosic binder, more preferably microcrystalline cellulose.

8. A process according to any preceding claim in which both d_d and d_i are in the range (0.7 to 1.5) d_a, preferably in the range (0.9-1.2) d_a.

9. A process according to any preceding claim in which the value of c_d is less than 0.3 c_a, preferably less than 0.2 c_a, and in which the value of c_a is preferably more than 1.0 kgf.

10. A process according to any preceding claim in which the deformable pellets are used in an amount of at least 15% by weight, more preferably at least 20% by weight of the total weight of pellets.

11. A process according to any preceding claim in which the amount by weight of disintegratable pellet is more than the amount by weight of deformable pellet.

12. A process according to any preceding claim in which tabletting is carried out at a pressure of at least 75 MPa, more preferably at least 100 MPa, preferably less than 150 MPa, more preferably less than 130 MPa.

Fig.1.

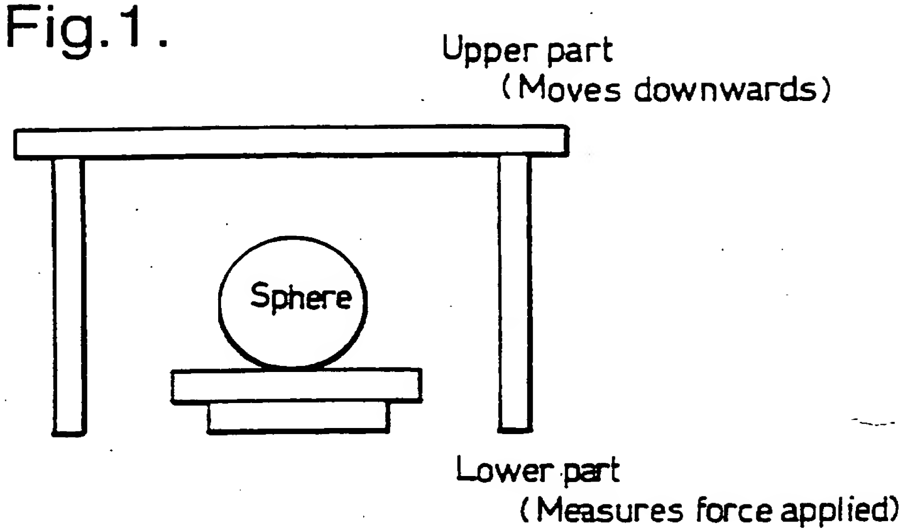

Upper part
(Moves downwards)
Sphere
Lower part
(Measures force applied)

Fig.2.

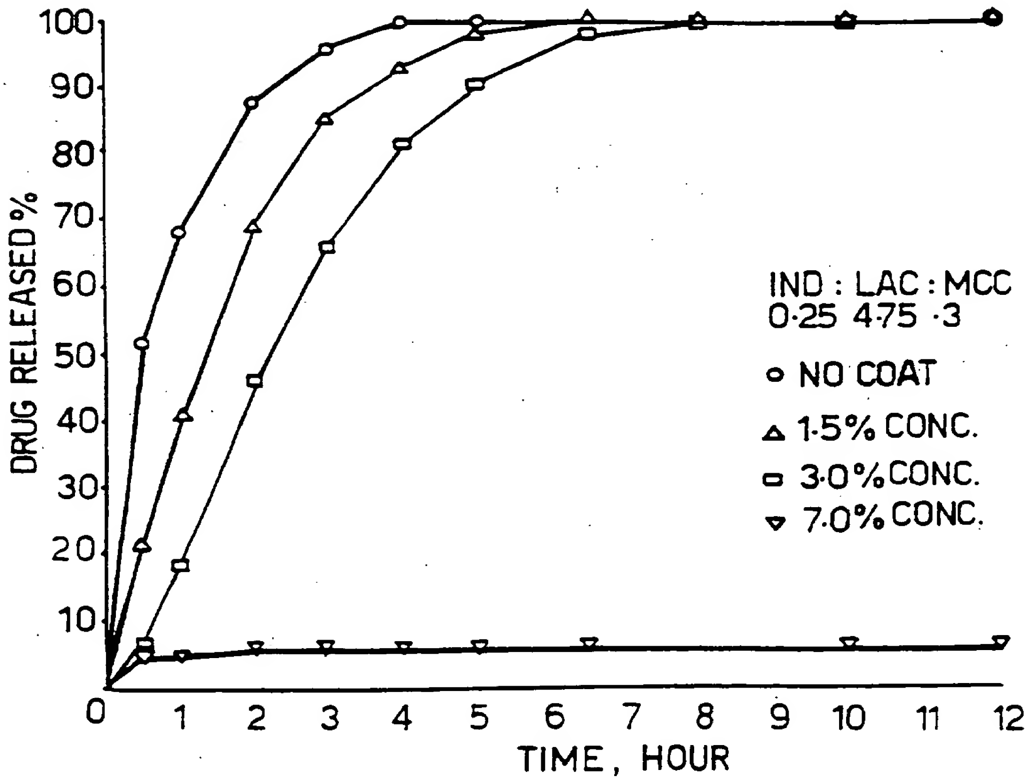

DRUG RELEASED %
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
TIME, HOUR
IND : LAC : MCC
0·25 4·75 ·3
NO COAT
1·5% CONC.
3·0% CONC.
7·0% CONC.

Fig.3.

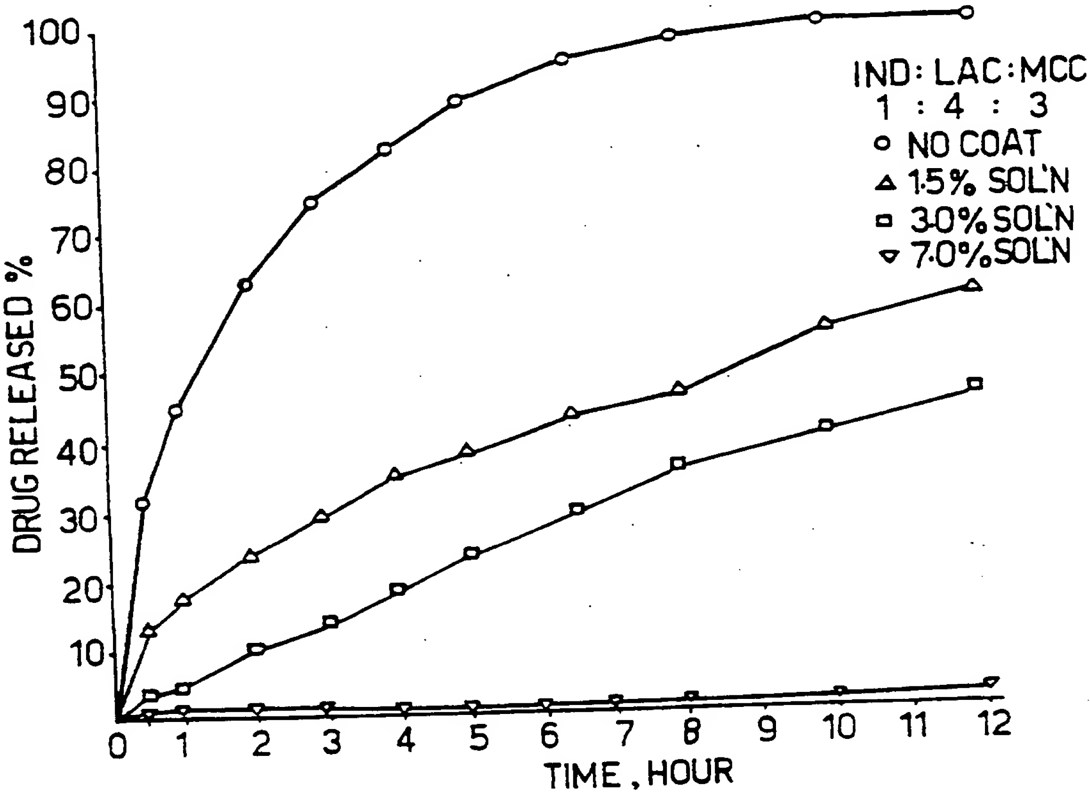
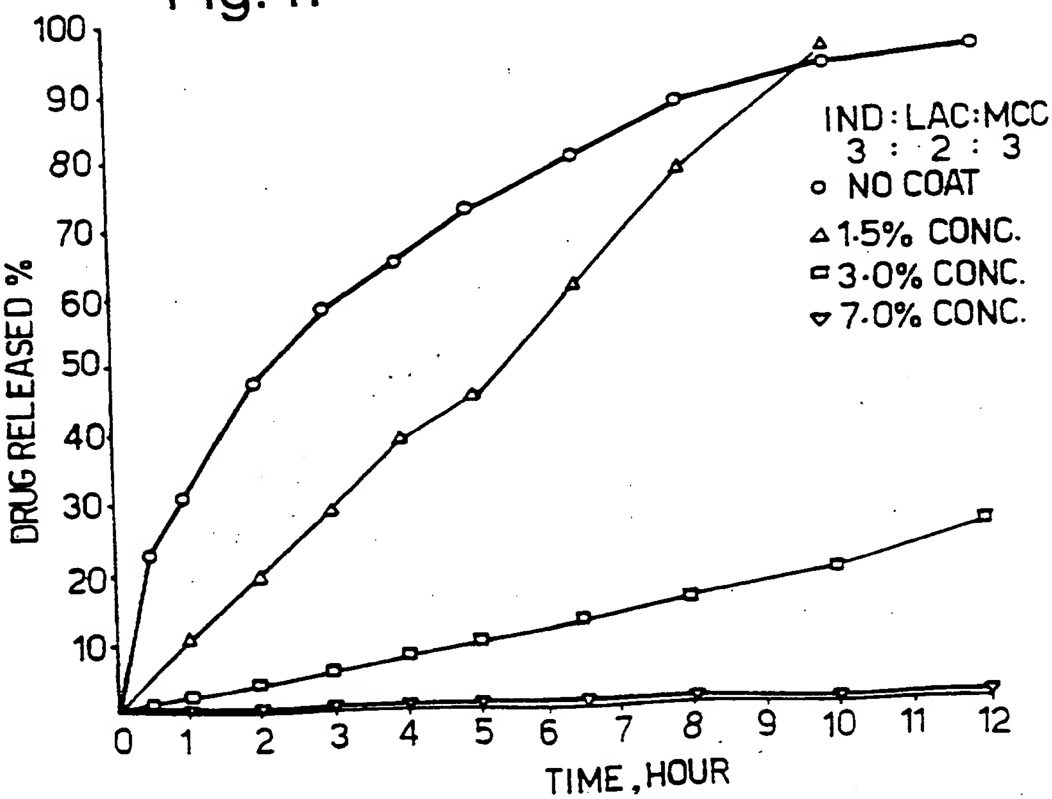

100
90
80
70
60
50
40
30
20
10
DRUG RELEASED %
0
1
2
3
4
5
6
7
8
9
10
11
12
TIME, HOUR
IND: LAC:MCC
1 : 4 : 3
NO COAT
1·5% SOL'N
3·0% SOL'N
7·0% SOL'N

Fig.4.


100
90
80
70
60
50
40
30
20
10
DRUG RELEASED %
0
1
2
3
4
5
6
7
8
9
10
11
12
TIME, HOUR
IND: LAC:MCC
3 : 2 : 3
NO COAT
1·5% CONC.
3·0% CONC.
7·0% CONC.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00068

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K9/16 A61K9/50 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 418 596 A (AMERICAN CYANAMID CO) 27 March 1991 see claims 1-9 ---	1-12
A	INT. J. OF PHARMACEUTICS, vol. 100, 1993, pages 81-92, XP000653243 CLARKE ET AL: "Gastrointestinal transit of pellets of differing size and density" see the whole document ---	1-12
A	PHARM. RES., vol. 10, no. 10, 1993, page S156 XP000653183 MOUNT ET AL: "Matrix cushioning ...." cited in the application * PT 6119 * see the whole document -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1997	22.05.97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/03068

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0418596 A	27-03-91	CA 2025714 A	22-03-91
		JP 3184911 A	12-08-91
		US 5283065 A	01-02-94